REMARKS

Applicants thank the Examiner for the Office Action of December 19, 2002. With the amendments above, we traverse the Section 112 issues raised by the Examiner without changing the scope of the claims.

With these remarks, Applicants traverse the rejection based on Section 103 in view of the Nishi, Taylor and Fang references. Those references are inapposite.

The Examiner does not appear to take issue with the irrelevance of Nishi as a reference ("Nishi does not teach the treatment of [neoplastic] lesions . . . ." see Office Action p. 4). So it is left to the other two references to bridge that considerable gap between Nishi and Applicants' claims.

Taylor is off target. It addresses cAMP phosphodiesterase, not cGMP-specific phosphodiesterase. The Examiner may be under a misapprehension about what Nishi's "cGMP-specific phosphodiesterase" is in applying the combination of art against Applicants' claims. As is understood by those skilled in the art and as used by Applicants, the term "cGMP-specific PDE" refers to a PDE that hydrolyzes cGMP but does not hydrolyze cAMP.

By contrast, some PDEs hydrolyze both cAMP and cGMP (e.g., PDE2 and PDE11). Others hydrolyze cAMP only (e.g., PDE4 and PDE7) and are called "cAMP-specific PDE." Still other PDEs are referred to as "calmodulin-dependent PDEs" (e.g., PDE1) or "cyclic GMP-inhibited PDEs" (e.g., PDE3); etc. These contrasting terms are well known to those skilled in the art. The word "specific" in this context does not require a "degree of specificity," it simply refers to a PDE that does not hydrolyze cAMP in the case of "cGMP-specific" or does not hydrolyze cGMP in the case of "cAMP-specific." In this light, the art cited by the Examiner is oblivious to or teaches away from Applicants' approach -- cGMP-specific PDE inhibition -- for reasons explained below.

It is clear that Taylor focuses on phosphodiesterase 1 ("PDE1") from the extensive discussion at column 17, lines 35 et seq., and Figure 23. He discusses the advantages of calcium regulation (in which PDE1 is implicated) and the hydrolysis of cAMP by that phosphodiesterase. One skilled in the art would clearly understand that approach to be a PDE1 approach. Also, Taylor focuses on tumor cell metastasis (see col.18), not tumor cell growth or death in primary tumors or in metastatic tumors. cGMP-specific PDE inhibition can lead to neoplastic cell death through a process known as apoptosis.

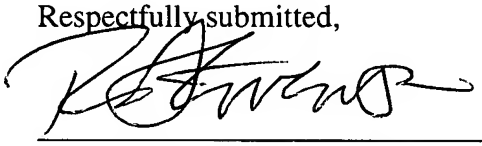
We believe that the Examiner completely misreads Fang. An examination of Fang's data reveals that zaprinast is completely inactive in inducing apopotosis. Compare the "Zap (10nM)" bar to the "control" bar in Figure B, and it is evident that zaprinast is not statistically different from control in terms of apoptosis. All Fang states is that cGMP "may participate in ANP-induced apoptosis" but the fact that zaprinast itself does not induce apoptosis better than control tells one skilled in the art that Fang believed that cGMP does not cause apoptosis. Indeed Applicants' assignee's data show that zaprinast does not induce paoptosis (see, e.g., U.S. Patent No. 6,200, 771 Table 4). Thus Fang actually teaches against the use of cGMP-specific PDE inhibitors to treat neoplasia

Thus, contrary to the Examiner's assertion, the cited references do not suggest Applicants' invention. They are oblivious to it or teach away from it.

Conclusion

This case is in condition to be allowed, which is respectfully requested in the next action.

Respectfully submitted,



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June 9, 2003

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